

PSJ17 Exh 27

Clinical Review

Robert B. Shibuya, M.D.

NDA 21-947 (000)

TRADE NAME (Fentanyl buccal tablets)

1. Lack of a comparator group
2. Use of concomitant medications, including at least one closely related compound (an opioid agonist) if not the fentanyl moiety itself
3. Generally declining clinical and functional status of patients with advanced cancer

7.1.7.1 Overview of laboratory testing in the development program

In the adequate and well-controlled study, labs were drawn at screening and at study termination. For the large majority of this period, patients were on OVF (only having received 3 doses of placebo). Since the blood draws may occur at a variable time compared to the last dose of OVF or placebo, it is difficult to attribute an abnormal laboratory finding to OVF, placebo, or a concomitant medication.

In the open-label, long-term studies, labs were to be drawn at screening and quarterly thereafter. However, at the time of data lock (3 October 2005), no data were available. This reviewer notes that the summary tables indicate that labs for all patients with cancer were included.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

As stated in 7.1.4.1, there are no placebo-controlled laboratory data.

7.1.7.3 Standard analyses and explorations of laboratory data

Descriptive statistics for the chemistry and hematology data were reviewed in detail (Section 2.7.4 Summary of Clinical Safety, Summary Tables 5.1.1. and 5.2.1, respectively). There were no significant changes from screening to end of study for the analytes studied.

7.1.7.3.1 *Analyses focused on measures of central tendency*

See Section 7.1.4.3.

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

This reviewer reviewed the shift tables prepared by the applicant (Section 2.7.4 Summary of Clinical Safety, Summary Tables 5.3.1 and 5.4.1 for the chemistry and hematology data. These tables indicated that a small number of patients developed laboratory abnormalities while on study. Those that were large in magnitude were generally captured in the context of serious adverse events and were discussed in the Deaths and SAE section of this review.

For those patients who developed laboratory abnormalities on study that were not associated with a SAE, again, due to the uncontrolled nature of the data, attributing the abnormality to OVF is not possible.

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7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See Sections 7.1.4.3 and 7.1.4.3.3.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

In the clinical program, vital signs were obtained per visit. Again, like the laboratory exams, attribution of cause in abnormalities from visit to visit is generally not possible.

7.1.8.1 Overview of vital signs testing in the development program

In the adequate and well-controlled studies (1 completed and 1 ongoing) vital signs were collected per visit (screening, randomization, end of open-label titration, and end of study).

In the open-label, long term studies, vital signs were collected monthly.

For both adequate and well-controlled and open-label studies, the first dose (100 mcg) of OVF was administered in the office with vital signs every 15 minutes.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Descriptive statistics for the vital signs were reviewed in detail (Section 2.7.4 Summary of Clinical Safety, Summary Table 6.1.1). When the means were compared at screening and end of study, no significant differences were noted. The vital signs taken every 15 minutes for one hour following the first, test dose in the office showed no clinically significant abnormalities.

REVIEWER COMMENT: The applicant compared the values at screening to end of study. The submitted analysis did not include an analysis of Visit 3, at the end of the open-label titration. This analysis was requested from the sponsor and provided. There

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were no significant differences noted between the vital signs at baseline and at Visit 3.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

As noted in the discussion of the laboratory exams, clinically significant outliers generally declared themselves as SAEs or AEs.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

See section 7.1.8.3.2.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not performed for any of the OVF trials.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

For this limited indication in patients with advanced malignancy, an assessment of carcinogenicity was not required. Furthermore, approximately half of the entire patient population already had cancer.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The fentanyl moiety has been classified Schedule II by the Drug Enforcement Agency. As such, it is subject to the highest levels of control at all points in the distribution chain. Fentanyl is a classic mu-opioid agonist and has the corresponding issues with tolerance, dependence, and abuse.

All instances of abuse, intoxication, and withdrawal that were submitted to this NDA and the corresponding IND (65,447) have been described in Sections 7.1.2 (SAEs) and 7.1.4. (Other search strategies). While it is distressing that certain portions of the population will abuse and misuse this product, the applicant has demonstrated that OVF is safe and effective for the

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proposed indication. Furthermore, the rate and nature of the incidents noted are typical for this kind of product when used in an outpatient setting.

As noted by Office of Drug Safety, the Risk Minimization Action Plan proposed by the Applicant should be strengthened in areas and this will be addressed during negotiations prior to the Division's Action on this product. The Controlled Substances Staff (CSS) consult is pending at the time this review is written. However, in internal discussions, CSS has expressed concern with regard to the abusability of this formulation.

This reviewer conducted an audit of drug accountability on approximately 20 patients. Given the simplified system of drug accountability in the open-label safety studies (the patient would retrospectively record the number of episodes of breakthrough pain/day and the number of tablets used/day), the drug accountability appeared acceptable. This reviewer does make note of the patient whose husband may have pilfered 12-18 tablets of OVF though.

7.1.14 Human Reproduction and Pregnancy Data

Fentanyl is pregnancy category C. The applicant has provided a summary of published literature regarding the effects of fentanyl on rat and rabbit gestation. The applicant has not conducted any other studies regarding the effects of OVF on pregnancy.

7.1.15 Assessment of Effect on Growth

Not applicable.

7.1.16 Overdose Experience

See section 7.1.4 for details.

Two patients attempted suicide while on an OVF study. One (patient #C25608-09915/88/8801) did not use OVF in the attempt, the other (patient #C25608/3040/BP/US/025/025003) had a history of depression and ingested a mixture of medications, including OVF. Neither patient completed their suicide.

One patient was found unconscious and cyanotic. She was diagnosed with a multiple drug overdose (alcohol, opioids, barbiturates (for which she did not have a prescription), and benzodiazepines). She denied suicidal ideation and admitted to using 6 OVF units in the previous 11 hours prior to being found. She was discontinued from the study.

One patient was found unresponsive and in respiratory distress. He was diagnosed with a multiple drug overdose and treated with naloxone. He was discontinued from the study.

On 19 April 2006, the Division received a 7-day alert. The husband of a patient on study 3040 (the open-label, long-term study in non-cancer patients) died, possibly due to OVF that was pilfered from his wife. Apparently, the patient's husband had a history of substance abuse. He was found dead soon after the patient was dispensed medication following her titration phase

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(800 mcg). The patient suspects that the death was due to an ingestion of OVF because 12-18 tablets of her supply were missing.

One patient became confused during the titration phase and self-administered 4 x 600 mcg tablets instead of 4 x 100 mcg as he had been instructed.

REVIEWER COMMENTS: Irresponsible use of opioids has always been a problem. In the opinion of this reviewer, the two cases where OVF may have been used in suicide attempts do not imply excess risk for a potent opioid like fentanyl.

With regard to the husband who possibly died from an overdose of his wife's study drug, the applicant will conduct a mandatory site-sponsor teleconference to emphasize the risks of abuse and diversion. In addition, the patient handout has been revised to emphasize that use of OVF by persons other than the patient can have fatal consequences.

The last case, where a patient became confused regarding which strength to self-administer, will be addressed in labeling and the medication guide.

7.1.17 Postmarketing Experience

OVF is not approved in any foreign countries.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Section 7.1 describes the trials, summary reports, and databases that were used to evaluate the safety of OVF.

7.2.1.1 Study type and design/patient enumeration

See Section 4.2 for a table enumerating the studies conducted in the development program.

7.2.1.2 Demographics

Aggregate descriptive statistics for the Phase I studies were not performed. In reviewing the demographic data for the individual studies, the mean age for the subjects was ~30 years. The preponderance of the subjects were Caucasian men (except for the studies conducted in Japanese subjects).

For the patients with cancer, the average age was 57 years with 77% of the patients being ≥65 years old. Half of the patients were men. The vast majority of the patients were White (85%) with Blacks composing the only other significant proportion (9%).

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For the patients with chronic pain not due to malignancy, the mean age was 48.2 years. Men composed 44% of the studied population. Ninety-four percent were White.

7.2.1.3 Extent of exposure (dose/duration)

The table following summarizes the successful dose used to treat an episode of breakthrough pain. Most of the patients required a strength in the middle portion of the to-be-marketed range.

Table 15: Summary of Dose Used To Successfully Treat A Breakthrough Pain Episode (all studies)

Mean dose/episode	# of patients (710 total)
<200	76
≥ 200 to < 400	147
400 to < 600	183
≥ 600 to < 800	204
≥ 800	79

The table following presents the total exposure data by total daily dose and duration.

Table 16: Total Patient Exposure By Dose and Duration (all studies)

	≤400	> 400 ≤800	> 800 ≤1600	> 1600 ≤2400	> 2400	Total
< 1 week	59	21	22	10	3	115
≥ 1 wk to < 2 wks	32	20	23	3	1	90
≥ 2 wks to < 1 mo	30	10	6	3	4	54
≥ 1 mo to < 2 mo	21	10	16	20	18	86
≥ 2 mo to < 3 mo	15	14	33	24	31	117
≥ 3 mo to < 4 mo	5	4	13	13	30	65
≥ 4 mo to < 5 mo	7	6	18	17	46	94
≥ 5 mo to < 6 mo	2	7	14	11	36	60
≥ 6 mo to < 7 mo	1	0	1	3	2	7
≥ 7 mo to < 8 mo	1	1	1	1	5	8
≥ 8 mo to < 9 mo	0	0	3	2	1	6
≥ 9 mo to < 10 mo	0	1	1	0	1	3
≥ 10 mo to < 11 mo	0	1	1	0	2	4
≥ 11 mo to < 12 mo	0	0	0	0	2	2
≥ 12 mo	0	0	1	2	6	9

While there were a substantial number of patients who were exposed to high total doses, there is a relative paucity of data beyond 5 months. Given the short expected lifespan of the intended population, this reviewer believes that this exposure is sufficient.

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7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical sources were used to evaluate the safety of OVF.

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

This is no post marketing experience with OVF.

7.2.2.3 Literature

To support its claims regarding the safety of fentanyl, the applicant relied upon published clinical studies using fentanyl and publications pertaining to breakthrough pain, cancer pain, and some of the endpoints used.

As stated in Section 7.1, the applicant's summary of the safety of fentanyl is supported, in part on the 30 journal articles submitted.

The literature search appears adequate, and to contain the information necessary to evaluate the previous experience with fentanyl.

7.2.3 Adequacy of Overall Clinical Experience

See Section 7.2.1 for more details regarding the extent of exposure to OVF. While the evaluation of safety was hampered by the lack of a clear comparator group, a parallel-arm, placebo-controlled study is not considered feasible for this patient population. In summary, with the exception of patients with mucositis in excess of a grade of 1, the overall exposure is sufficient to support a finding of safety in the proposed patient population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

Within the previously articulated limitations of the interpretability of the safety database, the routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

As a 505(b)(2) application, this section is not applicable.

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7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The primary areas of concern with OVF included local irritation/toxicity and whether the product could be managed safely in an outpatient setting given the pharmacokinetics of the product.

The development program clearly demonstrated that OVF causes signs and symptoms at the application site in a proportion of patients.

It appears that the applicant has demonstrated that the product can be safely titrated and dosed in an outpatient setting. This reviewer makes note of the one patient who became confused and self-administered 2,400 mcg instead of 400 mcg as he had been directed to do by the investigator, resulting in an SAE. This incident warrants dispensing of a limited number of strengths (perhaps a single strength) at a time during titration.

Furthermore, this reviewer notes that patients were contacted daily during the titration phase of all clinical trials. The proposed package insert

7.2.8 Assessment of Quality and Completeness of Data

Given the inherent limitations of the available safety data, the original NDA submission, together with additional information provided upon the Division's request over the course of the FDA review, provided sufficient data to conduct the safety review.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted the 120-day safety update on 5 January 2006. The safety section of this review incorporates all submitted safety data. A total of six further submissions were made in response to queries from the Division.

Table 17: Additional Clinical Submissions to NDA 21-947

Submission Date	Information Submitted
6 JAN 2006	Case report forms for protocol violations relating to patients who were on < 60 mg/day (morphine equivalents)
22 FEB 2006	Clarification of purpose of "Side Effects Diary" and specific reasons for discontinuation when coded "consent withdrawn"
24 FEB 2006	Additional clinical information for 4 patients
2 MAR 2006	Analysis of application site abnormalities
24 MAR 2006	Additional clinical information for several other SAEs
29 MAR 2006	Clinical study report for study 16 (mucositis PK study)

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7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall, patients reported typical opioid reactions (dizziness, sedation, nausea, vomiting, constipation). The only formulation-specific adverse events identified by this reviewer were the application site abnormalities.

There were no data limitations.

7.4 General Methodology

Methodology for the analysis of efficacy is discussed in Section 6.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The safety dataset was reviewed in toto.

7.4.1.2 Combining data

The safety dataset was reviewed in toto.

7.4.2 Explorations for Predictive Factors

Because of the complex medical regimens for most of these patients, and the fact that fentanyl was being dosed on a background of around-the-clock opioid, no exploration for predictive factors was conducted.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable.

7.4.2.3 Explorations for drug-demographic interactions

Not applicable.

7.4.2.4 Explorations for drug-disease interactions

Not applicable.

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7.4.2.5 Explorations for drug-drug interactions

Not applicable.

7.4.3 Causality Determination

See Section 7.1.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant has used a consistent titration/dose finding scheme (see Figure 1, on page 11 of this review) and, during the maintenance phase, has permitted the use of one additional tablet of OVF if sufficient relief was not achieved 30 minutes after the first tablet. Patients are instructed not to use additional OVF for 2-4 hours following the second tablet.

The dose titration scheme appears to be successful in eliminating patients who are intolerant of the product and those whose pain is not adequately alleviated by the maximum dose of OVF.

In the safety database, there was one instance of a significant safety problem during titration (the patient who mistakenly took 2,400 mcg instead of 400 mcg). This event occurred in study 3042, a trial similar in design to Studies 14 and 3039 except that it uses patients with low back pain. This incident emphasizes the need for close prescriber supervision during titration as well as limiting the number of strengths dispensed during the dose finding phase.

With the exception of the modifications proposed above in the dose finding phase, the safety database supports that the dosing regimen and administration scheme proposed is acceptable in an opioid-tolerant population.

8.2 Drug-Drug Interactions

As a 505(b)(2) application, no studies were conducted to address drug-drug interactions. The proposed package insert has standard warnings regarding cytochrome P450 3A4 inhibitors and inducers and warnings regarding CNS depressants. Dr. Chaurasia of the Office of Clinical Pharmacology and Biopharmaceutics recommended additional data regarding the effects of ritonavir on fentanyl metabolism.

8.3 Special Populations

Special populations were not specifically studied. Due to the diverse spectrum of malignancies in the patients enrolled, many had significant hepatic and pulmonary impairment. Again, given the limitations of the interpretability of the safety database, OVF does not appear to pose significant safety risks for the proposed patient population (except those at the application site).

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8.4 Pediatrics

The requirement for pediatric studies was deferred.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

The applicant has submitted a Risk Minimization Action Plan (RiskMAP) for OVF. The RiskMAP proposes the four established strategies for implementing the plan: Labeling, Education, Surveillance, and Intervention.

The plan identifies three goals. The goals and key strategies to be used to address the goals follow.


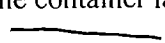
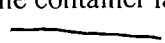
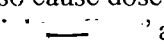
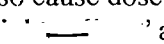
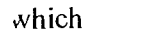
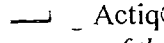
1. OVF is to be used by opioid-tolerant patients only.
 - a. The Black Box Warning clearly states that OVF is to be used only in opioid-tolerant patients.
 - b. The sponsor proposes to emphasize this in detailing to prescribers and in training and outreach to the pharmacy community.
2. No abuse, misuse, or diversion of OVF should occur.
 - a. Schedule II status
 - b. _____ warns that _____ giving OVF away is a crime.
 - c. Cartons and labels prominently feature the Schedule II status.
 - d. Various educational efforts
 - e. Extra medical education in geographical "hot spots."
 - f. Active monitoring system (RADARS, TESS, DAWN, NADDI).
 - g. Purchase of claims data
3. No accidental exposures should occur.
 - a. OVF is packaged in child-resistant, senior-friendly blisters.
 - b. Warnings to keep out of the reach of children on _____ labeling
 - c. Educational program (Dear Healthcare Provider letter) warning of the risk of accidental exposure to OVF.

The Office of Drug Safety (ODS) has completed its consult regarding the RiskMAP. ODS' input is paraphrased below. This reviewer's comments regarding each point appear in *italics*.

1. The RiskMAP does not address the potential for accidental exposure in children.
While this reviewer does not believe that OVF is any more attractive to children than any

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other tablet, in response to ODS' comments, the applicant has agreed to add appropriate warnings to the packaging and labeling.

2. The RiskMAP should include restricted promotion and marketing to physicians who care for cancer patients to minimize the potential for use in opioid-naïve patients. *This reviewer agrees. This product has a limited indication and should be promoted as narrowly as the regulations permit.*
3. The risk for medication errors has not been adequately addressed.
 - a. The fact that OVF is more bioavailable than Actiq® (approximately 50% more in the formal bioavailability study) is not prominent in the proposed labeling. *This reviewer agrees that this fact could be more prominent in the label. However, in the opinion of this reviewer, in the proposed patient population (opioid-tolerant patients), the difference of 50% in bioavailability is unlikely to cause significant morbidity. This reviewer is not certain that the risk to patients warrants inclusion in the Black Box Warning although if the applicant is amenable to doing so, it is acceptable.*
 - b. The proposed conversion scheme from Actiq® to OVF is overly complex and inconsistent with the known pharmacokinetic data. Specifically, if a patient is on . *This reviewer agrees that the conversion scheme from Actiq® should be simplified.*
 - c. The container labeling may cause confusion. For example,  is used for the  of Actiq® and the 100 mcg of OVF. ODS believes that this implies a dosing conversion. *No comment.*
 - d. Tablet colors may also cause dose confusion. Specifically, the lowest strength of OVF (100 mcg) is  and the highest strength (800 mcg) is . In addition, ODS objects to the fact that the 600 mcg OVF tablet is  which corresponds to the  Actiq® product. *This reviewer agrees. That two tablets, at the extreme range of the proposed strengths, may be confused is unacceptable. An 8-fold error in dose is likely to cause significant morbidity if not outright mortality. Unless this issue can be resolved prior to approval, this reviewer recommends that the 800 mcg strength not be approved until such time as the issue is rectified.*
4. OVF should have a Medication Guide, *Agree*
5. The educational plan should be modified.
 - a. The plan should ensure that prescribers understand the difference in bioavailability and that this product is not for use in opioid-naïve patients. *This reviewer believes that if information regarding the non-interchangeability with Actiq® is prominent in the Warnings, along with the indication, that is sufficient.*
 - b. The patient educational plan should emphasize that Actiq® and OVF are not interchangeable and to understand proper use of the drug. *Agree.*
6. The pharmacovigilance/evaluation plan should be modified.
 - a. The applicant should submit deaths, reports of exposure in children, and any medication error as a 15-day alert. *Agree*
 - b. The Quarterly Safety reports should include a section describing activity with regard to the RiskMAP. *No comment*

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- c. The applicant should provide more information about their survey methodology and how claims data will be used. *No comment*
- d. The applicant should consider using monitoring media surveillance, Key Informant Network, and Law Enforcement Drug Diversion Units. *No comment*

8.8 Other Relevant Materials

The following Divisions were consulted regarding the adequacy of the items below:

- Division of Medication Errors and Technical Support (DMETS): Proposed proprietary trade name.
- Division of Drug Marketing, Advertising, and Communications (DDMAC): Proposed Product Labeling
- Controlled Substances Staff (CSS): Risk Minimization Action Plan
- Division of Drug Risk Evaluation (DDRE): Risk Minimization Action Plan

Key recommendations include:

- Tradenames _____ have been found unacceptable by DMETS and DDMAC.
- Comments on the RiskMAP are covered in Section 8.7.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

The applicant found that OVF, in the dose range proposed for marketing and used as described in the clinical development program, was effective in providing relief from breakthrough pain in opioid-tolerant patients with chronic pain due to malignancy.

This reviewer agrees with the applicant's conclusion.

Safety

The analysis of safety was limited in many respects as discussed in Section 1.3.3 (lack of a clear comparator group, fentanyl was dosed in the context of around-the-clock opioids, overall poor health of approximately 50% of the safety population). Given these limitations, and the fact that this is a 505(b)(2) application referencing the fentanyl moiety that was first approved in 1968, the adverse event profile appears acceptable for this narrow indication. The cases of misuse and abuse, while regrettable, are an accepted risk when making potent opioids available to alleviate suffering in the legitimate cancer pain population.

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opinion that OVF should not be used in the outpatient setting is not supported with sound data or medical rationale.

CSS has identified certain safety concerns for both patients and non-patients. It is unequivocally true that this product has the potential to be abused and, if used improperly by patients or non-patients, could result in significant morbidity and mortality. However, CSS fails to acknowledge the potential benefits of OVF to alleviate the suffering of cancer patients. In this reviewer's opinion, many of CSS' conclusions overstate the risk of this product.

1. The time to peak plasma concentration probably occurs earlier with OVF compared to Actiq® (the pharmacokinetic data trend toward a earlier T_{max} although, in the opinion of this reviewer, the effect is not dramatic). That being said, some subjects achieved T_{max} within 20 minutes. Given the nature of breakthrough pain (sudden onset of intense, crescendo pain), if the T_{max} is truly sooner with OVF, the risk of opioid toxicity must be balanced against the therapeutic benefit of treating the breakthrough pain quickly which is really the whole issue in breakthrough pain. CSS does not consider this benefit.
2. All drugs are potentially fatal if used incorrectly or without proper monitoring. Since the labeled patient population is opioid-tolerant, there is a significant safety factor built in with regard to overdose. In fact, in the well-documented overdose during the clinical development program, the intended dose was exceeded by a factor of six. That is a minimum estimate of the overdose, since the planned four x 100 mcg dose represented a dose increase. The patient actually used four x 600 mcg tablets. Therefore, it was an overdose of 6-fold to 12-fold that resulted in hypoventilation and required medical assistance.
3. This statement is unqualified. OVF is approximately 50% more bioavailable compared to Actiq®. Correspondingly, the range of strengths to be marketed ranges from 100-800 mcg compared to 200-1,600 mcg. Again, the intended patient population is opioid-tolerant. With regard to the actual quantities of fentanyl on the market, CSS fails to note that, theoretically, the fact that OVF tablets contain half the amount fentanyl than Actiq® should result in half the amount of fentanyl being available on the market.
4. This reviewer agrees that OVF is highly abusable. Befitting its likelihood of being abused, it is a Schedule II drug. Furthermore, this reviewer favors a limited indication and limited promotion.
5. As per section 7.1.4 of this review, there were a total of four patients who experienced frank intoxication with OVF. Three of these patients experienced a poly-drug overdose. All of these events occurred to patients who were not in the cancer population. The irresponsible use of opioids would be expected to be higher in the non-cancer population than patients with cancer.
 - a. One patient had a history of depression and used a combination of medications including OVF in her uncompleted suicide.
 - b. One patient had a history of depression and one previous suicide attempt, was found down, and required resuscitation. Her toxicology screen included barbiturates, benzodiazepines, and presumably, alcohol and opioids. Against the instructions of her physician, she admitted to using 6 OVF tablets in the previous 11 hours.

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- c. One patient was found unresponsive and in respiratory distress after self-administering a combination of unknown amounts of immediate-release oxycodone, oxycodone/acetaminophen, and OVF.
- d. One patient became confused during titration and self-administered four x 600 mcg tablets instead of four x 100 mcg tablets as he was instructed by his physician. He required medical assistance for obtundation and respiratory depression.

The spouse of a patient (on a non-cancer study), may have died from the ingestion of OVF stolen from the patient. The deceased had a history of substance abuse. Whether OVF was the intoxicant is unknown at the time this review is written although the patient stated that she was missing 12-18 tablets.

As discussed in Section 7.1.16 of this review, this reviewer reviewed the drug accountability records in the case report forms for approximately 20 patients. Within the ability of a patient to recall tablet use, the drug accountability did not suggest significant diversion. This reviewer was informed by CSS that other incidents of stolen or missing OVF have been reported.

While issues of abuse are of great concern to this reviewer, in this reviewer's opinion, the cases represent irresponsible use of the drug in the non-cancer population or confusion during the titration phase. Since OVF will be indicated for cancer patients only, this should be less of a problem. Still, for the reasons articulated by CSS, this reviewer agrees that the Agency should make every effort to limit the likelihood of off-label use of OVF. The titration phase will require careful monitoring.

6. The Applicant's RiskMAP covers the accepted elements of risk minimization as best understood today. Without specific recommendations from CSS with regard to how the RiskMAP can be strengthened, along with data or a strong rationale demonstrating the effectiveness of these strategies, CSS' objections do not appear reasonable.
7. See 6.

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10 APPENDICES

10.1 Review of Individual Study Reports

NDA 21-947 is supported by a single adequate and well-controlled clinical trial, protocol 099-14.

Title: A Multicenter, Double-Blind, Placebo-Controlled Study of OraVescent® Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients

Primary Objective: To determine the clinical effectiveness of OraVescent® fentanyl when used to relieve breakthrough pain in opioid-tolerant cancer patients

Secondary Objective: To determine the safety and tolerability of OraVescent® fentanyl when used to relieve breakthrough pain in opioid-tolerant cancer patients

Study Design: Randomized, Double-Blind, Placebo-Controlled, Crossover, Safety and Efficacy trial.

Duration: The trial was designed for a maximum of 12 weeks (up to two weeks between screening and open-label titration, up to three weeks for an open-label titration, up to three weeks for the double-blind portion, and up to six weeks for a follow up visit). However, the study could have been conducted in as little as one to two weeks.

Sample Size: The protocol (dated 5 February 2004) was initially designed to complete approximately 90 patients. Amendment #1 (21 October 2004) decreased the sample size to 63 after reconducting a power analysis.

Inclusion Criteria:

Patients were to have met the following criteria:

1. Informed consent obtained
2. Is at least 18 years of age
3. Has a histologically documented diagnosis of a malignant solid tumor or a hematological malignancy causing cancer-related pain
4. Has an Eastern Cooperative Oncology Group (ECOG) performance status rating ≤ 2
5. Has a life-expectancy of at least 3 months
6. Has been receiving 60-1000 mg morphine/day or 50-300 μ g/hour transdermal fentanyl or opioid equivalent for at least a week for cancer-related pain
7. Is experiencing, on average, but not necessarily every day, 1-4 episodes of breakthrough pain per day that are adequately controlled with a stable dose of

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standard rescue medication, typically a fast-acting opioid, of which the patient will have an adequate supply throughout the study

8. Is willing and able (personally or with the help of a caregiver) to
 - a) evaluate and record pain intensity and pain relief
 - b) assess medication performance at specific times after dosing
 - c) record adverse events
 - d) record each instance of the use of study drug, standard rescue medication, and other medications in a patient diary
9. If female and of childbearing potential (not surgically sterile or ≤ 1 year after the onset of amenorrhea due to menopause)
 - a) has a negative serum pregnancy test
 - b) is not lactating
 - c) agrees to practice a reliable form of contraception or abstinence during the study.

Exclusion Criteria:

Patients were to have been excluded if any of the following applied:

1. Has an opioid or fentanyl intolerance
2. Is using intrathecal opioids
3. Is experiencing mucositis/stomatitis of Grade 2 or greater, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 either by clinical examination or functional/symptomatic criteria for the oral cavity [6]; or any other condition that could influence tolerance or absorption of study drug across the oral mucosa, e.g., xerostomia (note: if mucositis/stomatitis of Grade 2 or greater develops after the Titration Phase, the Investigator may choose to temporarily withhold dosing and should consult further with the Medical Monitor).
4. Has sleep apnea or active brain metastases with increased intracranial pressure
5. Has chronic obstructive pulmonary disease characterized by CO₂ retention
6. Has a recent history of substance abuse or neurologic or psychiatric impairment that would compromise data collection
7. Has had recent therapy (within 30 days) that would alter pain or responses to analgesics during the study such as palliative radiation therapy or a nerve block
8. Has renal or hepatic function test results at Screening outside the following limits:
 - a) serum creatinine must be ≤ 2.0 mg/dL or creatinine clearance calculated by Cockcroft-Gault formula must be ≥ 50 mL/min
 - b) serum total bilirubin must be ≤ 2.0 mg/dL
 - c) serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be ≤ 3 times the upper limit of normal (≤ 5 times the upper limit of normal if due to liver metastases)
9. Has received any other investigational new drug within 30 days of dosing
10. Is at risk of increased opioid side effects because of prior or concomitant medications (see Section 9.4.7)
11. Is at risk of significant bradyarrhythmia because of underlying heart disease

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12. In the opinion of the Investigator would not be likely to comply with all study requirements, including completing timed evaluations, recording in diaries, or returning diaries and drug supplies at each visit
13. Has primary source of breakthrough pain that is not cancer related.

Treatment:

Open-label Titration Phase: All patients were to have received Oravescent Fentanyl
Double-Blind Phase: Patients were to have received 10 numbered doses of study drug.
Seven of the doses were to have been active at the dose that was found to be efficacious during the open-label phase. Three were to have been placebo.
Patients were to have used the doses in the order specified.

Permitted Concomitant Medications:

Generally, patients were to have continued taking concomitant medications that were on stable dose and would not be expected to compromise the safe use of fentanyl. The only drugs specifically prohibited were monoamine oxidase inhibitors. These drugs were not to have been used within 14 days of initiation of study drug.

Rescue Medication:

Patients were to self-administer their usual rescue medication if the relief from the study drug is inadequate 30 minutes following administration. This was permitted during the open-label titration and double-blind phases.

Outcome Measures:

1. Pain Intensity [PI] (11-point numerical rating scale) pre-dose and 15, 30, 45, and 60 minutes post-dose
2. Pain Relief [PR] (5-point categorical rating scale) 15, 30, 45, and 60 minutes post-dose where 0 = none, 1 = slight, 2 = moderate, 3 = lots, 4 = complete
3. Patient Global Medication Performance Assessment (5-point categorical) 30 and 60 minutes post-dose in response to the question "Overall, how helpful is the study drug right now?" where 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent

Primary Efficacy Endpoint:

The primary efficacy endpoint was to have been the Summed Pain Intensity Difference at 15 and 30 minutes post-dose (SPID 30). PI was calculated as follows:

$$[(PI \text{ (pre-dose)} - PI \text{ (15 minutes post dose)}) + [(PI \text{ (pre-dose)} - PI \text{ (30 minutes post dose)})]$$

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Secondary Efficacy Endpoints:

- Pain Intensity Difference at each observation after dosing
- Pain Relief (PR) at each observation after dosing
- Total Pain Relief (TOTPAR), defined as the sum of the PR at 15 and 30 minutes post-dose
- Global medication performance assessment at 30 and 60 minutes post dose
- Incidence of using rescue medication after active and placebo tablets
- Time from dosing of study drug to the use of rescue after active and placebo tablets.

Safety:

Safety was to have been assessed by adverse event reporting by patients and Investigators, vital signs, physical examinations (including oral cavity exams), and clinical laboratory testing.

Exploratory Endpoints:

None

Study Visit Schedule (from page 28 of the protocol):

	Screening	Treatment		End of study
	Visit 1	Visit 2	Visit 3 ¹	Visit 4 ²
Procedures and assessments	Screening	Open-label dose titration period	Randomized double-blind treatment period	End of study or early termination
Informed consent	X			
Medical history	X			
Prior medication history	X			
Inclusion/exclusion criteria	X			
Clinical laboratory tests ³	X			X
Serum pregnancy test ⁴	X			X
Full physical examination ⁵ and neurological examination	X			X
Examination of oral mucosa	X	X		X
Vital signs measurements ⁶	X	X	X	X
Test dose (100 mcg) administered and tolerability observed (for 2 hr)		X		
Dispense/collect study drug ⁷		X		X
Provide/collect patient diary ⁸		X	X	X
Adverse event inquiry		X		X
Concomitant medication inquiry		X	X	X
Telephone contact with patient ⁹		X	X	
Randomization			X	
Study drug compliance check			X	X

¹ Randomized, double-blind treatment period was to be completed within 21 days (3 weeks).

² Patients who completed the study will be eligible to participate in an open-label long term safety study sponsored by Cephalon (study 099-15).

³ Clinical laboratory tests included serum chemistry and hematology.

⁴ Serum pregnancy tests performed on women of childbearing potential.

⁵ Height and weight were collected at visit 1, only.

⁶ Vital signs included sitting systolic and diastolic blood pressure, pulse, body temperature, and respiration rate.

⁷ Study drug was to be dispensed at visits 2 and 3. Used and unused study drug and packaging materials (empty bottles and empty blister cavities) were to be collected at visits 3 and 4.

⁸ Instructed patient how and when to perform the following assessments and record the results in the patient diary: pain intensity (immediately prior to and 15, 30, 45, and 60 minutes after administration of study drug); pain relief (15, 30, 45, and 60 minutes after administration of study drug); and global medication performance assessment (30 and 60 minutes after administration of study drug).

⁹ Study center personnel were to conduct daily telephone contact with patients to ensure that study procedures were being followed (ie, dosing and completion of diary).

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Statistical Analysis Plan and Definition of Analyzed Study Populations:

EFFICACY

The Intent to Treat Population (ITT) was defined as all patients who were dispensed double-blind medication (i.e. were able to achieve relief by one tablet of drug and experienced an acceptable adverse event profile).

The Modified Intent to Treat (mITT) population were those patients who received at least one dose of active and one dose of placebo and had at least one pain intensity score recorded for each of the two doses.

The Evaluable Population was the mITT patients with no major protocol violations and had the first three PI scores (0, 15, and 30 minutes) collected for at least one active and one placebo dose.

Missing data were to be imputed using a Last Observation Carried Forward method.

The Summed Pain Intensity Differences over the first 30 minutes (SPID30) were to be compared between the episodes treated with active versus those treated with placebo using an ANOVA model with treatment and center as fixed factors and patient as a random factor.

The secondary efficacy variables were analyzed similarly.

SAFETY

The safety population was defined as all patients who took at least one dose of study drug during the titration phase.

Adverse events were to be summarized separately and combined for the safety population using MedDRA terminology.

Vital signs were to be subjective to descriptive statistics.

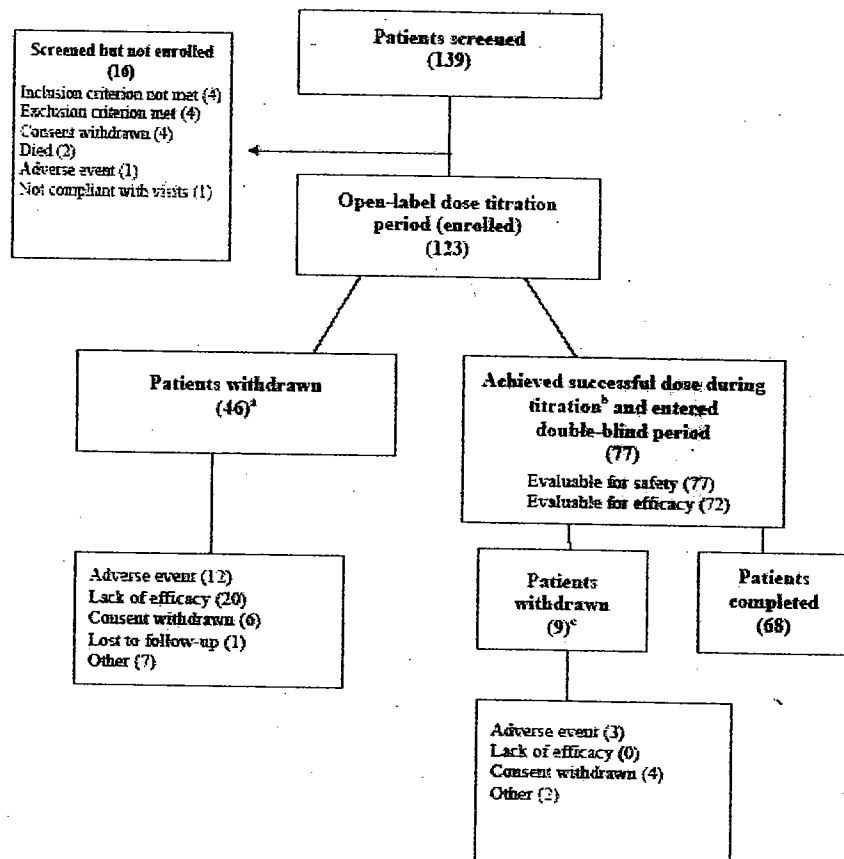
Protocol Amendment:

On 21 October 2004 (8 months after the initial protocol), Amendment 1 went into effect. The only modification was a recalculation of the power analysis where the sponsor concluded that only 63 patients would be required.

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RESULTS

Patient Exposure (taken from Figure 2 (page 54) of the Study Report)



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Explanations for patients who withdrew consent are shown in Table #9 (page 36 of this review)

Drop-Outs

After meeting screening criteria, 123 patients entered the titration phase. Of those 123 patients, 77 entered the double-blind phase. The large majority of patients dropped during titration were due to a lack of efficacy (43%) and adverse events (26%).

Of the 77 patients entering the double-blind phase, 68 completed the study. Seventy-two patients were evaluable for efficacy (had at least one episode treated with placebo and one treated with active and each episode had adequate endpoint data).

Protocol Deviations

The sponsor divided incidents of protocol noncompliance into deviations (minor in scope) or violations (those pertaining to inclusion/exclusion criteria, primary endpoint data, or GCP guidelines).

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There were three categories of interest in the "Protocol Violations" section.

1. The study report indicates that some patients did not follow the open label titration scheme correctly, i.e. start with 100µg then escalate to 200µg, 400µg, etc. However, review of the case report forms (CRF) available for 4 of the 8 pertinent patients revealed that the deviation was generally due to patient noncompliance and self-management. This reviewer did not identify any adverse events related to this protocol noncompliance. REVIEWER COMMENT: These protocol violations did not affect the findings in the study.
2. Thirteen patients were enrolled despite not meeting the minimum 60 mg (morphine equivalent) daily opioid requirement. In fact, one patient was enrolled despite a daily around-the-clock (ATC) morphine requirement of 5 mg. Three patients were on between 15 and 20 mg, 3 were on 30 mg, and 6 were on between 40 and 45 mg. Only two of these 11 patients discontinued and only one (#47004) discontinued due to an adverse event (constipation). REVIEWER COMMENT: Surprisingly, these patients who were on relatively low doses of opioids appear to have tolerated OVF well. These protocol violations do not appear to have affected the study findings.
3. Seventeen patients did not adhere to the study drug tablet administration order. The applicant deduced this because the diary sheets require patients to place an adhesive label corresponding to the dose actually taken. The one patient (#47002) who was noted to have taken study drug out of order and whose CRF was included had a nonsensical finding. The sponsor conducted a sensitivity analysis using the correct attribution of active/placebo. The noncompliance with tablet administration order did not significantly affect the outcome of the study. REVIEWER COMMENT: The applicant's explanation and sensitivity analysis show that these protocol violations were insignificant.

PRIMARY EFFICACY RESULTS

The primary efficacy variable was the summed pain intensity difference for the first 30 minutes post dose (SPID₃₀). The analysis was conducted on the 72 patients who met the definition of the full analysis set (used at least one active and one placebo dose and had at least one pretreatment score for each of these episodes).

The following table from the application shows descriptive statistics and the p-value for the primary endpoint where the pain intensity difference is based upon an 11-point (0-10) numerical rating scale (Source: Table 14 from the clinical study report, page 67).

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Table 14-1: Statistical Summary for Primary Efficacy Endpoint (Study 14)

Statistic	OVF (N=72)	Placebo (N=72)	p-value ^a
n	72	72	
Mean	3.2	2.0	
SD	2.60	2.21	
Median	2.6	1.3	
Min, max	-1.0, 12.7	-1.7, 9.7	
LS mean	3.0	1.8	<0.0001
SE of LS mean	0.12	0.18	

SOURCE: Summary 15.11, Listing 12.

^a P-value for the treatment comparison is based on a repeated measures analysis of variance (ANOVA) with treatment, center, and patient within center as factors.

SPID=summed pain intensity difference; OVF=ORAVESCENT fentanyl; SD=standard deviation; min=minimum; max=maximum; LS=least squares; SE=standard error.

The active doses were found to have a statistically significant larger summed pain intensity difference for 30 minutes compared to the placebo doses.

Secondary Efficacy Endpoints

Descriptive statistics and the p-values for the secondary endpoints are summarized in the table following.

Table 14-2: Summary of Statistics for Secondary Endpoints (Study 14)

Secondary Endpoint	Active (mean±sd)	Placebo (mean±sd)	p-value
SPID ₁₅ *	0.9 (1.14)	0.6 (.094)	0.0005
SPID ₄₅	6.5 (4.23)	3.9 (3.72)	<0.0001
SPID ₆₀	10.5 (5.99)	6.2 (5.49)	<0.0001
PID ₁₅ *	0.9 (1.14)	0.6 (.094)	0.0005
PID ₃₀	2.3 (1.54)	1.4 (1.36)	<0.0001
PID ₄₅	3.3 (2.7)	1.9 (1.7)	<0.0001
PID ₆₀	4.0 (2.04)	2.3 (2.0)	<0.0001
Pain Relief ₁₅ **	0.8 (0.62)	0.5 (0.59)	0.0005
Pain Relief ₃₀	1.4 (0.68)	0.9 (0.77)	<0.0001
Pain Relief ₄₅	1.9 (0.73)	1.1 (0.81)	<0.0001
Pain Relief ₆₀	2.1 (0.8)	1.3 (0.94)	<0.0001
Total Pain Relief ₁₅ **	0.8 (0.62)	0.5 (0.59)	0.0001
Total Pain Relief ₃₀	2.1 (1.23)	1.5 (1.28)	<0.0001
Total Pain Relief ₄₅	4.0 (1.83)	2.6 (2.01)	<0.0001
Total Pain Relief ₆₀	6.1 (2.48)	3.9 (2.88)	<0.0001
Global Medication Performance at 30 minutes**	1.4 (0.84)	0.9 (0.91)	<0.0001
Global Medication Performance at 60 minutes	2.1 (0.81)	1.3 (1.06)	<0.0001

*11-point Numerical Rating Scale

**5-point Categorical Scale

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Incidence of using rescue medication after active and placebo tablets

Rescue medication was used for 23% of the pain episodes treated with active compared to 50% of those treated with placebo. This results in a calculated relative risk ratio (that patients required rescue) of 0.47 (95% CI 0.37-0.60).

Time from dosing of study drug to the use of rescue after active and placebo tablets

Pain episodes treated with active drug had an average interval between study drug and the use of rescue of 57 minutes compared to 62 minutes for placebo.

REVIEWER COMMENTS:

The protocol-specified statistical analysis of the primary efficacy endpoint, SPID₃₀ showed a statistically significant difference in the mean SPID₃₀ between the episodes treated with OVF and those treated with placebo ($p < 0.0001$). Additionally, with the exception of the interval between study drug and rescue, these secondary efficacy endpoints support the conclusion that can be drawn from the primary efficacy endpoint, i.e. patients treated with the active drug experienced less pain intensity and greater pain relief compared to placebo.

However, the absolute difference in SPID₃₀ between the OVF and placebo-treated episodes was 1.2. This represented the sum of two pain intensity differences (the pain intensity collected at 15 and 30 minutes subtracted from the pre-treatment pain intensity). On its face, this absolute difference does not appear particularly convincing when this reviewer considered the clinical significance of this finding.

This reviewer conducted a review of the literature in this area. There was one journal article which directly assessed this question (Farrar et al¹). Farrar analyzed data from the Actiq® clinical trial, which used a study design essentially identical to Study 14.

Farrar concentrated on data from the open-label titration phase of the Actiq® trial (Part I). To review, during this phase, patients started with a single dose of the lowest to-be-marketed strength of Actiq®. Thirty minutes after dosing, if needed, patients were permitted to rescue with their standard rescue opioid. Farrar reasoned that this is an unequivocal, objective indicator of clinically relevant treatment success. Since breakthrough typically does not spontaneously resolve within 30 minutes, if the patient did not require rescue, it follows that the effect of the drug was clinically significant. If the patient required rescue, the intervention was inadequate. The titration phase was the most appropriate phase to analyze because there were a significant proportion of episodes where patients ultimately required rescue (and escalation to the next higher dose of Actiq®).

During the titration phase of this trial, data was available from 1210 episodes of breakthrough pain. In 349 instances, patients required rescue. Farrar devised standard 2 x 2 tables, similar to those used to assess diagnostic tests. For a description of this procedure, refer to Figure A1 following (reproduced verbatim from Farrar's article).

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Figure A1: Example of how sensitivity, specificity, and accuracy were calculated using a 2 x 2 matrix.

Definition of sensitivity, specificity, and accuracy^a

PID% ^b	No additional rescue dose	Yes additional rescue dose	Totals
≥33	a = 632	b = 106	738
<33	c = 229	d = 243	472
Totals	861	349	n = 1210

^a Values calculated for a ≥33% change in pain intensity. Sensitivity, $a/(a + c) = 73.4\%$; specificity, $d/(b + d) = 69.6\%$; accuracy, $(a + d)/n = 72.3\%$.

^b PID% ≥ 33% cut off is a positive outcome compared with the positive gold standard of not using an additional rescue dose.

From these 2 x 2 tables, Farrar was able to calculate sensitivity, specificity, and accuracy. Farrar conducted this analysis for six variables:

1. % Maximum TOTPAR over 60 minutes
2. %PID at 30 minutes
3. Absolute PID at 30 minutes
4. Pain Relief at 30 minutes
5. SPID60
6. Global Assessment at 60 minutes

Farrar used different cutoff values through a wide range to generate multiple 2 x 2 tables with their respective calculated sensitivity, specificity, and accuracy percentages. He selected the optimal cutoff values first by selecting the highest accuracy but using the balance of sensitivity and specificity as a secondary consideration. On the basis of this analysis, Farrar concluded that the optimal cutoff values that imply clinical significance for pain trials are 33%, 33%, 2, 2, 2, and 2, respectively, for variables 1-6. He conducted a logistic regression analysis of the Part II (double-blind portion consisting of 7 active doses and 3 placebo) which supported the cutoff values selected on the basis of the Part I (open-label titration phase) data.

— This reviewer compared data from Study 14 in the OVF NDA submission to Farrar's recommendations. The results (based on averaged data) are summarized in the table following.

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Table 14-3: Summary of Statistics from Study 14 Compared to Cutoff Values from Farrar

Parameter	Cutoff	Trial Data	Meets Cutoff
% Max TOTPAR over 60 minutes	33%	6.1/16=38%	Yes
%PID at 30 minutes	33%	2.3/6.9=33%	Yes
Absolute PID at 30 minutes	2	2.3	Yes
Pain Relief at 30 minutes	2	1.4	No
Summed Pain Intensity Difference over 60 minutes	2	10.5 (2.6 points per measurement)	Yes
Global Assessment at 60 minutes	2	2.1	Yes

FINAL ASSESSMENT OF EFFICACY:

On the basis of:

- The high degree of statistical significance for a primary endpoint that, at this time, is considered the most appropriate for an analgesic,
- The fact that essentially all of the secondary endpoints support a finding of efficacy,
- That the data from Study 14 meet five of six of Farrar's criteria,
- That the data regarding rescue medication use after OVF and placebo support the notion that OVF has greater analgesia than placebo, and
- That the pain relief versus time data appear similar to the approved drug, Actiq®,

this reviewer concludes that OVF provides a statistically significant, clinically relevant level of analgesia for the proposed indication.

SAFETY FINDINGS

Deaths, serious adverse events, and adverse events leading to discontinuation are discussed in the safety section of this review. Briefly, in the context of the interpretability of these data, review of those cases does not raise concern about the safety of this drug above and beyond other formulations of fentanyl or other potent opioids appropriate for this indication. Similarly, no safety signals of concern were identified for the adverse events.

OTHER CLINICAL TRIALS

Three other protocols are pertinent to this application. One (Study 3039) is an adequate and well-controlled study, very similar to Study 14. Protocols 099-15 and 3040 are open-label, long-term, safety studies that are enrolling patients with breakthrough pain in the setting of cancer pain (Study 15) and non-malignant pain (Study 3040).

A short discussion of how Studies 14 and 3039 differ and a description of Studies 15 and 3040 follows.

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Protocol C25608/3039/BP/US

Study 3039 is essentially identical to 099-14 with the following significant exceptions.

- The timing of efficacy assessments has been modified. In Protocol 14, pain intensity and pain relief were to be recorded predose, and 15, 30, 45, and 60 minutes post dose. These variables are to be measured predose and 5, 10, 15, 30, 45, 60, 90, and 120 minutes post dose.
- The primary efficacy endpoint for Study 3039 is a SPID₆₀ compared to a SPID₃₀ for Study 14.

Study 3039 was ongoing at the time of filing and will contribute safety data only in support of this application.

Protocols 099-15 and C25608/3040/BP/US

These are open-label, long-term, safety studies examining the safety of Oravescent Fentanyl in patients with breakthrough pain in cancer patients (Study 15) and patients with pain not due to cancer.

Briefly, Study 15 rolls over patients from Studies 14 and 3039 and enrolls new patients. As such, the inclusion and exclusion criteria are similar. For patients new to the investigational drug, the protocol dictates the standard titration procedure. Following the titration phase (where appropriate) or completion of Studies 14 or 3039, patients enter the maintenance phase of Study 15. During the maintenance phase, patients record the number of breakthrough pain episodes and number of tablets used each day along with a global assessment of study medication.

Patients are seen in the office at approximately monthly intervals where adverse events are solicited, patient vital signs are collected, drug accountability is done, and new drug is dispensed. At months 3, 6, 9, and end of study, physical exams, lab tests, and oral mucosa exams are conducted in addition. The study is designed to run for 12 months although many of these cancer patients are expected to die before completing the entire trial.

Study 3040 studies patients with non-cancer pain. Other than not enrolling patients with cancer, the inclusion and exclusion criteria are similar to Study 15. Patients will undergo the standard titration scheme to an effective and tolerated dose. Assessments of efficacy are secondary objectives and include the Brief Pain Inventory-Short Form, modified Oswestry scale, Profile of Mood States, Short-Form Health Survey (SF-36) for Quality of Life, Goal Attainment Scale, and Sleep Questionnaire. Similarly to Study 15, patients will be seen at approximately monthly intervals for safety evaluations and to exchange study materials such as questionnaires and drug product.

These trials were ongoing at the time of filing and the 120-day safety update.

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Table A1: Deaths Due Directly to the Underlying Malignancy (e.g. tissue destruction due to expansion of the primary or of a metastasis)

Pt ID	Study #	Comments	Narrative
02007	14	Study drug d/ced 11 days before death	
06002	14	Study drug d/ced 10 days before death	
29001	14	Study drug d/ced 17 days before death	
47002	14	Study drug d/ced 88 days before death	
02001	15	Study drug d/ced 44 days before death. Lung CA experienced COPD exacerbation, pneumonia, progression of disease.	
02008	15	Study drug d/ced 6 days before death. Respiratory failure in pt w/ NSC lung CA.	
02011	15	Study drug d/ced 79 days before death	
02015	15	40 yo woman with stage IV cervical CA experienced progressive deterioration in health (pleural effusion, edema, neutropenia, pain, decubitus ulcers)	
02020	15	Study drug d/ced 40 days before death	
02021	15	Study drug d/ced 24 days before death	
04010	15	Study drug d/ced 1 day before death	
27008	15	Study drug d/ced 10 days before death	
29007	15	Study drug d/ced 16 days before death	
31010	15	61-year old man with pancreatic cancer metastatic to the liver experienced worsening course due to disease progression and expired on study drug.	
39002	15	Study drug d/ced 16 days before death	
44002	15	Study drug d/ced 12 days before death. Pt. w/ NSC lung CA, aspirated/pneumonia.	X
46004	15	Study drug d/ced 8 days before death	
47001	15	Study drug d/ced 16 days before death	
47005	15	71-year-old man with prostate CA experienced SAE of brain met, ascites, pleural effusion and died on day 181 due to progression of the prostate CA.	
47007	15	65-year-old man with metastatic pancreatic CA experienced a rapid deterioration in health culminating in death due to progression of disease.	
49001	15	Study drug d/ced 34 days before death	
51005	15	Study drug d/ced 21 days before death	
53004	15	Study drug d/ced 5 days before death	
53005	15	Study drug d/ced 3 days before death	
58001	15	Study drug d/ced 30 days before death. Woman with carcinomatosis including brain mets (terminal event).	
59001	15	Study drug d/ced 17 days before death. Prior to death, pt had developed nausea and vomiting, neutropenia, pyrexia, atrial fibrillation.	
59004	15	55-year-old man with metastatic prostate CA. Experienced anemia, constipation, cancer pain, asthenia, edema, vomiting, jaundice treated with multiple anti-neoplastic drugs and analgesics. Experienced a decrease in the level of consciousness with normal ammonia. Narcotics held but clinical status continued to deteriorate, culminating in death. study drug d/ced 3 days before death.	X
68002	15	Study drug d/ced 83 days before death	

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Pt ID	Study #	Comments	Narrative
304003	15	Study drug d/ced 26 days before death	
306008	15	Study drug d/ced 8 days before death	
313001	15	Study drug d/ced 2 days before death	X
305001	3039	Study drug d/ced 28 days before death	
309004	3039	Study drug d/ced 21 days before death	
350001	3039	Study drug d/ced 19 days before death	

Table A2: Deaths Due to Complications of the Underlying Malignancy (e.g. sepsis secondary to leukopenia, secondary to chemotherapy)

Pt ID	Study #	Comments	Narrative
34002	14	Sm bowel fistula...Study drug d/ced 4 days prior to SAE and 73 days prior to death	
47003	14	Hypercalcemia...Study drug d/ced 4 days before death	X
57003	14	Multiorgan failure. Study drug d/ced 4 days before death	X
02010	15	Man w/ metastatic prostate CA on 100 mcg OL OVF developed bowel obstruction and died due to complications.	
04002	15	Study drug d/ced 15 days before death	
18002	15	Study drug d/ced 37 days before death	
26004	15	Study drug d/ced 5 days before death	
34008	15	46-year-old woman with neuroendocrine CA experienced deteriorating clinical course, multiple SAEs (acute renal failure secondary to ABX, neutropenia, progression of abdominal tumor, etc). Study drug d/ced 40 days prior to death.	
41002	15	Study drug d/ced 11 days before death	
44001	15	Pt. w/ pancreatic CA, h/o small bowel obstruction, experienced decreasing oral intake had to go on TPN, died.	
49004	15	Study drug d/ced 59 days before death. Pt developed pneumonia 15 days post d/c study drug and died of the pneumonia 44 days later.	
302003	15	Man with CML and multiple medical problems had terminal admission for severe confusion. Review of study drug diary revealed that he only used 14 doses of study drug in the 7 days prior to admission and one dose the day prior to admission.	X
305003	15	Study drug d/ced 7 days before death	
306007	15	Study drug d/ced 11 days before death	
351003	15	Study drug d/ced 2 days before death. Had MS changes, encephalopathy.	

Table A3: Deaths Due to Causes Other than the Underlying Malignancy

Pt ID	Study #	Comments	Narrative
02028	15	Study drug d/ced 3 days before death due to CVA.	
78003	15	Study drug d/ced 2 days before death. Death due to intracerebral hemorrhage due to warfarin overdosage.	
021008	3040	Study drug d/ced 28 days before death. Pt. did not have malignancy	

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Table A4: Serious Adverse Events Due to the Underlying Malignancy or Comorbid States

Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
02023	14			X	Hospitalization	Cancer pain, dehydration, pneumonia	SAE 4 days after last dose of study drug.	
38002	14			X	Hospitalization	Cancer pain	Pt. only took one dose of study drug; insufficient time to meet obligations.	
46003	14			X	Hospitalization	Pathologic compression fracture		
02029	15			X		Pain and cough	Pt not on study drug at the time of SAE.	
04006	15			X	Hospitalization	CNS mets and convulsions	Pt. discontinued soon after hospitalization for seizures secondary to brain mets.	
17033	15			X	Hospitalization	Chest pain, fever, pneumonia, esophageal ulceration	Chest pain and fever (initial events leading to hospitalization), occurred after study drug d/ced.	
34011	15			X	Hospitalization	Recurrent and residual paraganglioma of the spine		
39001	15			X	Hospitalization	Metastases to bile ducts, syncope, dehydration, jaundice, nausea, vomiting	Pt. is continuing on study.	
43006	15			X	Hospitalization	Pt with adenoCA of the GI tract and bone mets developed severe abdominal pain requiring hospitalization.	Pt. discontinued when hospitalized for pain.	

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Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
51008	15			X	Hospitalization	Man with lymphoma, status post radiation to the supraclavicular area, hospitalized multiply for severe bleeding-dx radioosteonecrosis with fistula formation.	Pt. remains on study.	
58003	15			X	Hospitalization	Subdural hematoma and brain mets		
59003	15			X	Hospitalization	Woman with metastatic gastric CA hospitalized for hypercalcemia and progression of disease 20 days after last dose of study drug.	Withdrawn from trial per investigator's discretion.	
77001	15			X	Hospitalization	Progression of lung CA	Pt discontinued.	
77002	15			X	Hospitalization	Pain, progression of lung CA	Pt discontinued.	
305004	15			X	Hospitalization	Man with metastatic lung CA and multiple medical problems including COPD, + smoker developed pneumonia and required hospitalization.		
302003	3039			X	Hospitalization	Edema, CHF	Due to imatinib (per investigator)	

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Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
304007	3039			X	Hospitalization	Obstructive jaundice	Pt. discontinued for nausea (likely due to obstructive jaundice).	
309003	3039			X	Hospitalization	Hemoptysis	Study drug stopped 22 days prior to SAE.	
312001	3039			X	Hospitalization	Small intestinal obstruction	Recurrent SBO in patient with recurrent endometrial cancer c/b rectovaginal fistula	

Table A5: Serious Adverse Events Due to Complications of the Underlying Malignancy or Comorbid States

Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
38001	14			X	Hospitalization	DVT	Pt. only took one dose of study drug.	
44004	14			X	Hospitalization	Asthenia (left leg weakness), thrombocytopenia, Candida UTI	Sxs resolved w/ treatment.	
53004	14			X	Hospitalization	Asthenia (generalized weakness), volume depletion, pain	Sxs resolved w/ treatment.	
02006	15			X	Hospitalization	abdominal pain, hypercalcemia, nausea, vomiting, chest pain, femur fracture, dehydration, diarrhea	Pt with NSC lung CA developed multiple SAEs while on study drug.	
02024	15			X	Hospitalization	pneumonia, pulmonary embolus	Pt w/ gastric cancer and liver mets developed PE and pneumonia.	
04011	15			X	Hospitalization	Pathologic hip fracture, seroma (required debridement)	Pt. has continued on study	

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Pt ID	Study	Related to OV??			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
18004	15		X		Hospitalization	Pneumonia, confusion	76 yo man with multiple myeloma of vertebra and squamous cell CA of ear. Pt was hospitalized for pneumonia on study day 32 which resolved. On study day 51, he experienced moderate confusion that the investigator felt was probably due to study drug. Study drug stopped due to confusional state.	
26003	15			X	Hospitalization	pneumonia, pulmonary embolus	Study drug stopped due to the pneumonia and PE.	
29002	15			X	Hospitalization	Pulmonary infiltrates	URI and pulmonary infiltrates in pt with liver CA and bone mets. Pt is continuing in study.	
34015	15			X	Hospitalization	Pt with lung and cervical small cell, metastatic to bone and liver, hospitalized for dehydration. Treated with IV hydromorphone, hyperalimentation, and RBC. Workup showed progression of disease.		
43005	15			X	Hospitalization	Woman with metastatic breast CA, h/o DVT hospitalized for tremors of the hands and legs. Had a second hospitalization for dyspnea, pulmonary embolus, confusional state.	Pt. is continuing on study.	X
44004	15			X	Hospitalization	Urinary tract infection, diarrhea		

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Pt ID	Study	Related to OV?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
44005	15			X	Hospitalization	Aspiration pneumonia, cardio-pulmonary arrest (due to Zosyn), Zosyn-induced anaphylaxis, hypoxia, pleural effusion		X
47010	15			X	Hospitalization	Man with mesothelioma hospitalized for dehydration, pneumonia, and abdominal pain. Had a second hospitalization for subclavian vein thrombosis.	Pt. remains on study.	
47012	15			X	Hospitalization	Deep venous thrombosis	Pt. is continuing on study.	
68001	15			X	Hospitalization	Woman with ovarian cancer hospitalized with severe anemia, hypotension, hypercalcemia.	Pt. had "moderate mouth sores" and application site ulcer.	
306004	15			X	Hospitalization	Man with multiple myeloma and multiple medical problems including a history of fever, 60 pound weight loss, immobility hospitalized for pneumonia.		
354001	3039			X	Hospitalization	Pancytopenia, anemia, obstructive jaundice	Pt discontinued study drug use after neutropenia on cytotoxic chemo.	
001008	3040		X		Hospitalization	Woman with arachnoiditis developed neurogenic bladder 5 days after last dose of study drug.	Opioids can cause neurogenic bladder.	
007002	3040			X	Hospitalization	Pt with severe rheumatoid arthritis hospitalized for sepsis.		

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Table A6: Serious Adverse Events Due to Causes Other than the Underlying Malignancy or Comorbid States

Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
49003	14			X	Hospitalization	Coronary artery dz		
34001	15			X	Hospitalization	aortic aneurysm, CAD		
34003	15			X	Hospitalization	Superior vena cava syndrome with jugular vein and brachiocephalic thrombosis secondary to port-a-cath placement.		
37002	15			X	Hospitalization	Pt with non-Hodgkin's lymphoma and cirrhosis secondary to Hepatitis C developed mental status changes. Hospitalized and diagnosed with severe hepatic encephalopathy.		
38005	15			X	Hospitalization	A-fib and pneumonia		
64002	15			X		Woman with multiple myeloma and history of depression and anxiety hospitalized with worsening anxiety and depression.		
65004	15			X	Hospitalization	Woman with breast CA admitted for elective breast reconstruction.	Pt. had soreness at application site.	
88001	15			X	Hospitalization	Man with prostate CA attempted suicide. OVF not used in suicide attempt.	Pt. discontinued from study upon hospitalization.	
304005	15		X		Hospitalization	Woman with multiple myeloma and multiple medical problems including hypertension, experienced several episodes of presyncope and syncope, resulting in hospitalization.	Patient's use of OVF increased during period of syncope.	X
302003	3039			X	Hospitalization	Edema, CHF	Due to imatinib (per investigator)	
313001	3039			X		Anemia	SAE occurred prior to taking any study drug.	
318001	3039			X		Cholecystitis	SAE occurred prior to taking any study drug.	
02717	3040			X	Hospitalization	Inguinal lymph node infection.		
003010	3040			X	Hospitalization	Gastroenteritis		
004009	3040			X	Hospitalization	Cholelithiasis		
004018	3040			X	Hospitalization	Man with chronic low back pain hospitalized for small bowel obstruction.		X

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Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
005001	3040			X	Hospitalization	71 year old woman with low back pain hospitalized with atrial fibrillation.		
006007	3040			X	Hospitalization	Cholelithiasis		
007003	3040			X	Hospitalization	Man with chronic pain hospitalized for pain follow a motor vehicle accident.		
012002	3040			X	Hospitalization	Woman with CRPS hospitalized for TIA.		
013009	3040			X	Hospitalization	Woman with chronic low back pain hospitalized for severe irritable bowel syndrome.	Investigator opined that SAE not related to OVF. Diary shows that pt continued to take ~5 tablets of OVF throughout hospitalization.	
013021	3040			X	Hospitalization	Tib-fib fracture		
013033	3040			X	Hospitalization	Man with pain due to chondromalacia hospitalized for two episodes of colitis.		
019004	3040			X	Hospitalization	Man with chronic low back pain hospitalized for migraine.		
021006	3040			X	Hospitalization	Man with chronic low back pain and h/o HTN, TIA, carotid endarterectomy, coronary stent hospitalized for ischemic leg.		
024034	3040			X	Hospitalization	Woman with chronic pain due to traumatic injury hospitalized with angina.		
024041	3040			X	Hospitalization	Woman with chronic headache hospitalized with vomiting, abdominal pain, dehydration.		
025001	3040			X		Woman with chronic low back pain experienced chest pain, dyspnea, nausea, and syncope.	Pt. remains on study.	
025003	3040			X	Hospitalization	Woman with low back pain and h/o depression found down (suicide attempt).		X
025015	3040				Hospitalization	Woman with chronic headache hospitalized for dehydration due to minimal to no PO intake x 48 hours resulting in syncope, delirium, and fall. Pt was diagnosed with celiac disease on this hospitalization.	Pt. remains on study.	X

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Pt ID	Study	Related to OVF?			Nature	Description	Comments	Narrative
		Definitely	Possibly	Not				
025017	3040			X	Hospitalization	Man with chronic low back pain and degenerative disc dz C1-C6 experienced severe cervical spinal cord injury and asthenia.		
027003	3040			X	Hospitalization	Traumatic laceration (due to spinning fan) and cellulitis.		
027008	3040			X		Woman with CRPS and history of HTN and MI experienced three episodes of severe chest pain and dyspnea ± nausea.		
027024	3040			X	Hospitalization	Femoral fracture		
030003	3040			X	Hospitalization	Asthma exacerbation		
030006	3040			X	Hospitalization	Hemorrhage post cone Bx.		
031005	3040			X	Hospitalization	Woman with chronic low back pain and hypertension hospitalized with atrial fibrillation.		
031016	3040			X	Hospitalization	Woman with chronic low back pain and mesenteric vasculitis hospitalized with severe pulmonary hypertension.		X
034037	3040		X			Man with chronic pain due to nephrolithiasis and migraine experienced a seizure.	Opioids can cause seizures. Patient was on study drug when he experienced a "serious convulsion of severe intensity." However, pt. was on chronic meperidine which is more epileptogenic.	X

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Table A7: Discontinuations due to Adverse Events

Pt ID	Study	Description of AE	Related				Comments
			Definitely	Probably	Possibly	Not	
01001	14	Vomiting and abdominal distension in woman with widespread metastatic dz (breast primary)			X		Investigator considered not related.
04004	14	Dizziness after a 600 mcg dose during titration.		X			Dizziness resolved after study drug stopped.
06007	14	Fatigue and dysarthria during titration phase.			X		
10001	14	Moderate vomiting in patient on ondansetron for h/o nausea during titration phase.	X				Resolved after study drug stopped.
17002	14	Weakness and tremor (pt w/ h/o prostate CA, weakness, and fatigue).			X		
18007	14	Moderate drowsiness after taking the test dose.	X				
31005	14	Stomatitis and ulceration at application site	X				Resolved w/o sequelae.
32004	14	Nausea and dizziness temporally related to OVF dosing.	X				Resolved w/o sequelae.
38004	14	Migraine post dosing in patient without h/o migraine.			X		
44007	14	Nausea and dizziness temporally related to OVF dosing.	X				
47004	14	Application site ulcers	X				
012008	3040	Patient with chronic low back pain, depression, and h/o multiple drug sensitivities developed scalp rash.			X		
017001	3040	Application site blisters, moderate nausea, dizziness, and headache.	X				
019003	3040	Moderate to severe nausea and vomiting during titration phase...temporally related to multiple doses of OVF.		X			
352001	3039	Woman with multiple medical problems including breast and renal CA developed sedation during OVF titration.	X				
354003	3039	Woman with multiple medical problems including carcinosarcoma and leiomyosarcoma developed dizziness, visual disturbance, tremor during OVF titration.	X				
11001	15	Woman with long CA developed nausea and vomiting on study drug.		X			
31004	15	Woman with multiple myeloma developed application site erythema, ulcer, pain, edema, pustule, thrush, facial swelling	X				

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Pt ID	Study	Description of AE	Related				Comments
			Definitely	Probably	Possibly	Not	
32006	15	Woman with multiple myeloma developed nausea on study drug.		X			
51002	15	Man with cancer pain and Charcot-Marie-Tooth Disease developed palpitations, not actually related to the time of OVF dosing but while he was on trial.				X	
57002	15	Woman with breast and uterine cancer and bone mets developed stomach discomfort, related to study drug dosing. The patient also reported hallucinations and dysgeusia. It was not clear whether the hallucinations and dysgeusia were related temporally to use of OVF.			X		
77005	15	Woman with breast cancer developed nausea and vomiting related to use of OVF.	X				
78001	15	Woman with lung cancer developed moderate diarrhea while on the trial.			X		
311005	3039	Woman with laryngeal CA s/p left hemilaryngectomy and radical neck dissection developed buccal mucosal discoloration and nausea.		X			
43007	15	Woman with metastatic breast CA developed dizziness, nausea and headache after dosing with OVF.		X			Sxs resolved post D/C.
313003	15	Man with tongue cancer developed dizziness on OVF. The dizziness persisted for at least 23 days following OVF discontinuation.				X	
001007	3040	Woman developed nausea and dizziness during titration phase.		X			
002002	3040	Patient developed application site ulcer (resolved after drug was stopped).	X				
005008	3040	Woman developed tachycardia and anxiety during titration phase. These sxs resolved after drug discontinuation.			X		
007004	3040	Patient developed vomiting during the titration phase.		X			
010003	3040	Patient developed nausea and vomiting during titration.		X			
010005	3040	Woman with chronic low back pain developed generalized pain during the study.					
010014	3040	Woman with chronic pain due to fibromyalgia developed nausea, hyperhidrosis, and "moodiness" on study drug.					
011019	3040	Patient developed anorexia and nausea during maintenance period.		X			
013015	3040	Patient developed nausea and vomiting during titration.		X			

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Pt ID	Study	Description of AE	Related				Comments
			Definitely	Probably	Possibly	Not	
013025	3040	Man developed somnolence during titration.	X				
013040	3040	Man developed blurred vision, nausea, dizziness, and headache during titration.		X			
015008	3040	Woman developed headache in maintenance phase.		X			
016005	3040	Man developed moderate sedation in maintenance phase.		X			
016007	3040	Woman developed sedation in titration phase.		X			
016009	3040	Woman developed urticaria during titration phase.				X	Fentanyl does not cause mast cell degranulation and rarely causes urticaria. Patient was on ATC oxycodone and hydromorphone, both of which can result in histamine release.
017008	3040	"Allergic reaction"					No other information available
018028	3040	Patient developed fatigue on OVF.			X		
019006	3040	Dizziness. Rash also reported but occurred 8 days after study drug discontinued.		X			
019012	3040	Vomiting, hallucination, and anxiety during titration phase.		X			
019018	3040	Vomiting, dizziness, nausea, and euphoria on study drug.		X			
022004	3040	Patient injured meniscus while in maintenance phase.				X	
023004	3040	Patient developed nausea and vomiting during titration.		X			
024008	3040	Patient developed nausea during titration.		X			
024015	3040	Patient developed anxiety during titration.		X			
024038	3040	Application site ulcer		X			
025020	3040	Vomiting and application site ulcer		X			
030011	3040	Nightmare, hyperhidrosis, and tinnitus during titration.		X			
031002	3040	Man developed nausea during titration phase.		X			
032007	3040	Woman developed multiple complaints (application site pain, muscle twitching, nausea, blurred vision, hyperhidrosis, depression, pain, headache) on OVF		X			Review of CRF showed multiple vague constitutional complaints over a 3 week period. All resolved without sequelae.
033011	3040	Vomiting, nausea, application site pain during titration.		X			
033013	3040	Dizziness and glossodynia during maintenance.		X			
034052	3040	Pruritic rash during titration.				X	Fentanyl does not cause mast cell degranulation and rarely causes urticaria. Patient was on ATC morphine and oxycodone, both of which can result in histamine release.
036001	3040	Sedation during titration		X			
037003	3040	Nausea, vomiting, tremor, and hyperhidrosis during titration.		X			

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Pt ID	Study	Description of AE	Related				Comments
			Definitely	Probably	Possibly	Not	
037005	3040	Drug eruption occurring after a 100 mcg dose and blurred vision occurring 5 days after the last dose of study drug.		X			
037008	3040	Nausea and vomiting during titration.		X			
039002	3040	Confusion and application site pain occurring during titration.		X			
039004	3040	Hypesthesia and blurred vision during titration.			X		

Summary

Not applicable. Study 14 was covered previously in the Appendix. Safety data from Studies 3039, 3040, and 15 are included in the safety review.

10.2 Line-by-Line Labeling Review

See addendum to this review for information regarding labeling for the product.

References

¹Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287-294.

²Girmenia C, Moleti ML, Cartoni C, Cedrone M, De Gregoris C, De Sanctis V, Giovannini M, Latagliata R, Niscola P, Romani C, Rondinelli MB, Mandelli F. Management of infective complications in patients with advanced hematologic malignancies in home care. Leukemia 1997;11:1807-1812.

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/s/

Robert Shibuya
6/28/2006 11:29:53 AM
MEDICAL OFFICER

Sharon Hertz
6/28/2006 06:53:06 PM
MEDICAL OFFICER

I concur with the recommendation to approve this product.
As noted in Dr. Shibuya's addendum, outstanding concerns
have been adequately addressed to support approval of
the 100 mcg through 800 mcg tablets with
the modifications to the tablet color.